THERMOMETRIC TITRATIONS OF SOME DIVALENT CATIONS WITH DIETHYLENETRIAMINEPENTAACETIC ACID

A Thesis

Presented to

the Faculty of the Department of Chemistry

Appalachian State University

In Partial Fulfillment

of the Requirements for the Degree

Master of Arts

by

John Andrew Barrett

December 1967

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CATIONS WITH DIETHYLENETRIAMINEPENTAACETIC ACID

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by

John Andrew Barrett

Approved by:

James E. Johnson, Acting
Chairman of Thesis Advisory Committee

Curtis Williams
Dean of the Graduate School

Donald L Wright
Major Professor

ACKNOWLEDGEMENT

The author wishes to express his sincere appreciation to Dr. D. L. Wright for his advice, encouragement and assistance throughout the course of this investigation.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Thermometric Titrations of Some Divalent Cations with Diethylenetriaminepentaacetic Acid

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John Andrew Barrett

Thermometric titrations of Hg^{2+}, Pb^{2+}, Cd^{2+}, Mg^{2+}, Ca^{2+}, Mn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+} with diethylenetriaminepentaacetic acid have been investigated. In most instances the accuracy of the analysis was one per cent or less. Difficulties encountered in the standardization of Co^{2+} and Zn^{2+} are given as the reasons for the larger errors in the analyses of these two ions. In addition the following mixtures, Ca^{2+} and Mg^{2+}, and Ca^{2+} and Cd^{2+}, have been directly determined by thermometric titrations. The error in these determinations was generally less than two per cent.

Also, a mixture of Hg^{2+} and Pb^{2+} was determined by indirect means. The Hg^{2+} was titrated in the presence of Pb^{2+} in strongly acidic solution while in weakly acid solution the sum of the two ions was determined. The Pb^{2+} was then calculated from the difference.

The effect of the pH on the effective stability constants of the various metal chelates was found to limit the component ions determinable in a mixture. This investigation also shows that the order of titration of metal ions in a mixture is dependent upon the pH of the solution.

CHAPTER I

INTRODUCTION

Introduction to Chelation:

Complex formation has been employed in classical chemical analysis for over a century. However, until two decades ago, only a few applications had been made in classical titrimetric analysis. Flaschka (3) suggests that this is because most complexation reactions do not meet the following basic requirements:

(a) The complex reaction must be stoicheiometric so that a basis of calculation exists.
(b) The rate of reaction must be sufficiently fast.
(c) The stability of the complexes must be sufficiently high, otherwise a sharp endpoint cannot be obtained because of dissociation.
(d) The complex reaction should involve as few steps as possible so that a sharp endpoint is assured.
(e) A simple method for the location of the endpoint must be known.
(f) No precipitation should occur during the titration to avoid such complications as co-precipitation, adsorption, and other phenomena often accompanying precipitation.

Only a few cases of complexation involving monodentate ligands meet all of these requirements sufficiently to be practical for titrations.

The introduction of polyaminocarboxylic acids, the first of which was ethylenediaminetetraacetic acid (EDTA) has revolutionized metal ion analysis. These polyaminocarboxylate ligands meet all of the requirements stated by Flaschka and now have been applied to the analysis of over 50 elements. Since the introduction of EDTA as a chelating agent for metal ions by

Schwarzenbach in 1946, many other similar chelating agents have been introduced. Among these are trans-cyclohexanediaminetetraacetic acid (CyDTA), N-hydroxyethylethylenediaminetriacetic acid (HEDTA), ethyletherdiaminetetraacetic acid (EEDTA), ethyleneglycol bis-(β-aminoethyl ether)-N, N'-tetraacetic acid (EGTA), and diethylenetriaminepentaacetic acid (DTPA). These reagents also have found uses in other fields such as biology and medicine for diverse functions including the removal of accumulations of various metal ions in the body, antidotes for some types of poisons, and the study of iron metabolism in humans.

The most difficult problem involving the use of these chelating agents in volumetric analysis has been the selection of suitable methods of endpoint detection. The most popular approach has been the use of metallochromic indicators. This method employs a trace quantity of a complexing dye which exhibits one color in a "metallized" form and a different color in the "unmetallized" form. At the equivalence point, the chelating agent removes the metal ion form the metal-dye complex with a resulting color change.

One disadvantage of metallochromic indicators is that often the color change will be blocked by traces of Cu^{2+}, Co^{2+}, Ni^{2+}, and Fe^{3+}. Reasons for the color change blocking are (1) slow rates of reaction between the metal ions and indicators and (2) unusually high stabilities of the metal-indicator complexes.

The mercury indicator electrode has been frequently employed as a method of endpoint detection in potentiometric titrations (13, 15). This technique is not as restrictive as visual titrations with metallochromic indicators because the endpoint of almost all titrations can be detected under a wide variety of conditions without serious difficulties.

However, it is less convenient.

Other techniques of endpoint detection which have been used in chelometric analysis include photometric (17), conductometric (4), high frequency (5), amperometric, chronopotentiometric (14), and thermometric methods.

Introduction to Thermometric Titrations:

A thermometric titration utilizes the enthalpy change of the reaction involved to locate the endpoint. It has been defined by Jordan (7) as "a titration in an adiabatic system yielding a plot of temperature versus volume of titrant." The procedure consists of delivering the titrant from a buret into a solution contained within a thermally insulated vessel, and observing the change in temperature of the solution either continuously or after each addition of titrant.

The first published paper on thermometric titrations was by Bell and Cowell (1) in 1913 in which they reported the thermometric titration of citric acid with ammonium hydroxide. The full scope and power of this method of endpoint detection was demonstrated by Dutoit and Grobet (2a.) when they applied thermometric titrations to a variety of systems including acidimetry, precipitation, and complexation.

Linde, Rogers, and Hume are responsible for the recent success of this method. In 1953 they replaced the Beckmannthermometer, used in previous work, with a thermistor and used a constant flow-rate buret to permit automatic recording of curves for various acid-base titrations (12). Since this development many applications of thermometric titrations have been made. These include (1) titration of weak monoprotic acids (9), (2) titration of colloidal electrolytes in detergent analysis (10), (3) complexation with EDTA (8), and (4) titrations in non-aqueous solvents (11, 20).

Table I

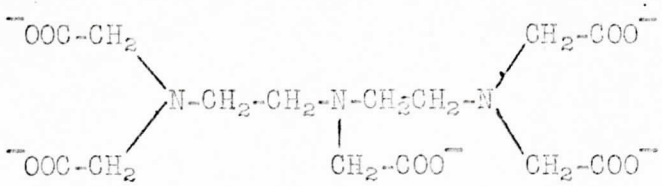
Heats of Formation for DTPA and EDTA Chelates

Metal Ion	ΔH, kcal/mole	
	DTPA	EDTA
Mg^{2+}	+3.6±0.3 (19)	+3.1 (2)
Ca^{2+}	-6.1±0.4	-5.8 (2)
Mn^{2+}	-7.5±0.4	-5.2 (2)
Co^{2+}	-9.5±0.4	-4.1 (2)
Ni^{2+}	-11.2±0.5	-7.6 (2)
Cu^{2+}	-13.4±0.5	-8.2 (2)
Zn^{2+}	-10.6±0.5	-4.5 (2)
Cd^{2+}	-12.4±0.5	-9.1 (2)
Hg^{2+}	-23.6±0.8	-19.2 (19)
Pb^{2+}	-18.8±0.6	-13.1 (2)

Figure 1

A Comparison of Structures of EDTA and DTPA (19)

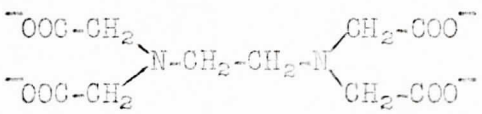
DTPA



$pk_1 = 10.55$, $pk_2 = 8.60$, $pk_3 = 4.26$, $pk_4 = 2.41$, $pk_5 = 2.08$

$T = 20°C$ and $\mu = 0.10$

EDTA



$pk_1 = 10.26$, $pk_2 = 6.16$, $pk_3 = 2.67$, $pk_4 = 2.00$

$T = 20°C$ and $\mu = 0.1$

The first application of thermometric titrations to metal ion analysis using a polyaminocarboxylic acid as a titrant was made by Jordon and Alleman (8). They titrated Pb^{2+}, Cd^{2+}, Cu^{2+}, Ni^{2+}, Ca^{2+}, Zn^{2+}, Co^{2+}, and Mg^{2+} with EDTA and from their data calculated the heats of formation of the various metal-EDTA complexes. Jordon and Alleman believed this to be the first successful titrimetric method for the determination of heats of reaction in aqueous solutions.

Statement of the Problem:

An inspection of data obtained by Wright, Holloway, and Reilley (19) on the heats of reaction of several of the polyaminocarboxylic acids with divalent cations, showed that the heats of reaction for the metal-DTPA complexes were significantly higher than the corresponding metal-EDTA complexes. The heat of reaction data for both DTPA and EDTA chelates is summarized in Table 1. Also, Holloway and Reilley have shown that DTPA forms more stable metal chelates than EDTA (6). This can be explained by a comparison of the structures of DTPA and EDTA. The presence of eight coordinating groups in DTPA versus the six coordinating groups in EDTA increases the probability of chelation. Also, because DTPA exhibits more basic character than EDTA, the metal-ligand bond strengths are stronger in the metal-DTPA chelates than in the corresponding metal-EDTA chelates.

An analysis of this thermodynamic data indicates that thermometric titrations of divalent metal ions with DTPA should be practical. It was the purpose of this study to determine if such titrations were feasible and, if so, under what conditions.

CHAPTER II

TITRATION OF METAL IONS WITH DTPA

Materials and Apparatus Used:

Reagent grade chemicals were used throughout this investigation except for the DTPA (assay of 98% minimum) which was obtained from the J. T. Baker Chemical Company, Phillipsburg, New Jersey.

All the metal ion solutions were prepared from the corresponding metal nitrates and distilled water and standardized against EDTA using procedures given in references (3), (16), and (18). To suppress hydrolysis approximately 0.5ml of 15M HNO_3 was added to some of the metal ion solutions. All metal ion solutions were approximately 0.1M.

The DTPA solutions were prepared by adding the appropriate amount of solid sodium hydroxide to dissolve the solid DTPA in the required volume of distilled water. The DTPA was standardized against a standard zinc solution prepared from zinc metal according to the procedure in reference (3). Two preparations of DTPA were required. The first solution was 0.999M and the second was 1.004M..

All thermometric titrations were carried out at room temperature and the temperature changes were recorded by a Beckmann thermometer. The titrant was introduced by using a 10ml buret.

All thermometric titrations were performed in a 265ml Dewar flask which was closed with a stopper having appropriate holes for inserting the Beckmann thermometer and the buret tip.

Experimental Procedure:

Holloway and Reilley (6) have reported that the effective stability constants of the metal-DTPA chelates are at a maximum in definite ranges

Table II

Effective Stability Constants of Metal-DTPA Complexes at the Most Favorable pH Values (6)

Metal Ion	log K	pH
Mg^{2+}	9.0	8.2- 9.8
Ca^{2+}	10.7	7.0-10.0
Mn^{2+}	15.5	4.0- 7.0
Co^{2+}	19.0	
Ni^{2+}	20.2	3.0- 5.0
Cu^{2+}	21.0	3.0- 4.5
Zn^{2+}	18.8	5.0- 6.0
Cd^{2+}	19.0	5.0- 6.0
Hg^{2+}	27.0	
Pb^{2+}	18.6	5.0- 7.0

of pH. This data is given in Table 2. Because the chelate must be stable in order to be useful in analysis, the pH of the metal ion solution being titrated was adjusted to the proper value before titration. In some instances the solution was made very basic because the DTPA solution, with a pH of 6, lowered the pH of the solution as it was added during the titration. The Hg^{2+} solution required the addition of a large amount of 15M HNO_3 to prevent hydrolysis because in this titration, the DTPA raised the pH of the solution.

The procedure necessary for adjusting the pH was dependent on the metal ion involved. The addition of 15 drops of 15M HNO_3 in each sample were required to prevent hydrolysis of Hg^{2+} and allow chelation to take place. Cd^{2+} and Zn^{2+} could be titrated successfully only after enough ammonia buffer of pH = 10 was added to dissolve the precipitate which was formed upon addition of the first few drops of buffer. Cu^{2+} required that the solution be neutralized with sodium hydroxide before titration. Ca^{2+} could be determined only after the addition of 2.0ml of ammonia buffer of pH = 10. About 0.1 gram of ascorbic acid was added to the Mn^{2+} solution to prevent oxidation to the higher oxidation states. When oxidation of Mn^{2+} takes place a brown precipitate (probably MnO_2) is formed which reacts very slowly with DTPA. The pH of the Mn^{2+} was adjusted to a pH of 10 with ammonia after addition of the ascorbic acid. Pb^{2+}, Ni^{2+}, and Mg^{2+} were titrated without adjusting the pH.

In addition to the adding of reagents to adjust the pH, 5ml of distilled water were added to each sample taken so that the volume of the sample was large enough to cover at least half of the mercury reservoir of the Beckmann thermometer. In most instances, the sample was in a total volume of about

10ml. The size of each sample was approximately 0.5 millimoles, producing a final concentration of each sample of about 0.05M.

After the sample was placed in the titration flask and the thermometer was inserted, 15-20 minutes were allowed before beginning the titration to allow the thermometer and the rest of the system to come to thermal equilibrium. No effort was made to have the sample and titrant at exactly the same temperature. A difference in temperature of the two changed only the shape of the resulting curve and not the endpoint.

The titrant, DTPA, was approximately twenty times more concentrated than the metal ion solution in order to minimize changes in the heat capacity of these systems caused by dilution and was added in increments of 0.10ml. After each addition of titrant the flask was swirled several times to stir the solution. This method of stirring eliminated any temperature rise from stirring such as would occur if a stirring rod or mechanical stirrer were used. The small volume used made this type of stirring very efficient.

Readings of the thermometer were made initially and two minutes after each addition of titrant. This was the optimum amount of time to wait because this allowed both for complete chelation to take place and the thermometer to respond to the temperature change accompanying this chelation. Also, this length of time permitted the titration to be performed quickly enough to minimize the possibility of significant heat loss from the Dewar flask.

From the data of each titration a plot of thermometer reading versus volume of titrant was constructed. When a sharp break in the curve at the endpoint was not obtained, the sections of the curve having different slopes were extrapolated to determine the endpoint.

CHAPTER III

RESULTS AND CONCLUSIONS

Results:

The following single ions have been titrated: Hg^{2+}, Pb^{2+}, Cd^{2+}, Zn^{2+}, Mn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Ca^{2+}, and Mg^{2+}. In all of the titrations except for those with Zn^{2+} and Co^{2+} an error of less than one per cent was obtained. It is believed that the error in the titrations of Zn^{2+} and Co^{2+} (between 2 and 3%) was caused by difficulties in determining the color change of the indicator used in the standardization titrations of the metal ion solutions. The results for three titrations of each of these two ions have a high enough degree of precision to support this conclusion.

Those ions which have the more exothermic heats of reaction with DTPA gave the better titration curves. Although these curves were not necessarily more accurate, they were easier to extrapolate to determine the endpoint because they produced a sharper break in the curve at the endpoint.

The direct titration of mixtures presented a problem in that only those ions which form stable chelates in the same narrow pH range could be determined. In a given pH range the effective stability constants for both chelates must be large enough that the DTPA will react with both metal ions and at the same time the difference between the two effective stability constants must be large enough that the titration will occur in a step-wise manner, one metal ion at a time. This places a restriction on suitable ions to be titrated in a mixture. Probably a more sensitive temperature detecting device such as a thermistor would allow for measurement of smaller temperature changes and thus might widen the possible combinations of ions determinable in a mixture.

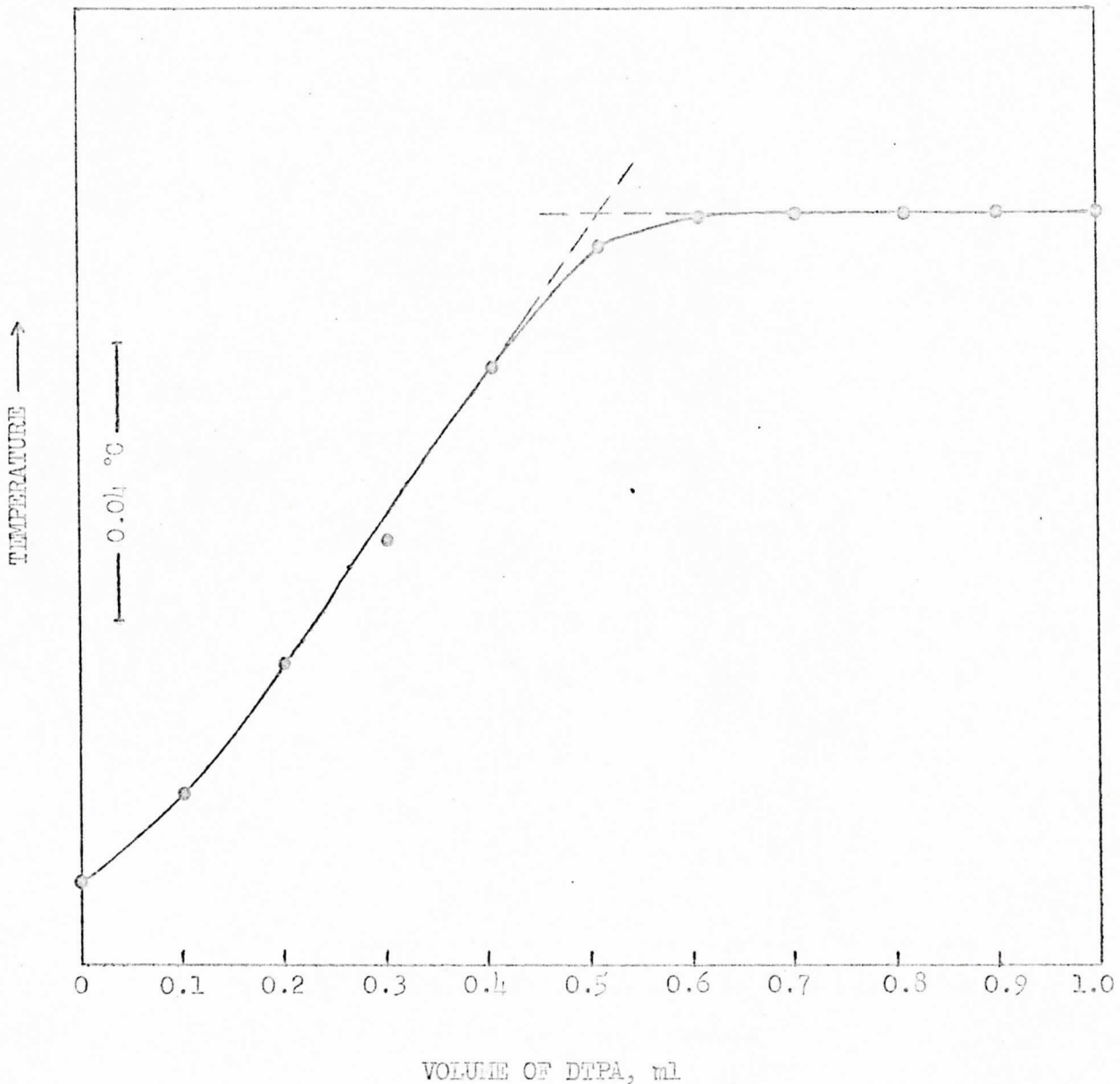


Figure 2

Titration of Hg^{2+} with DTPA

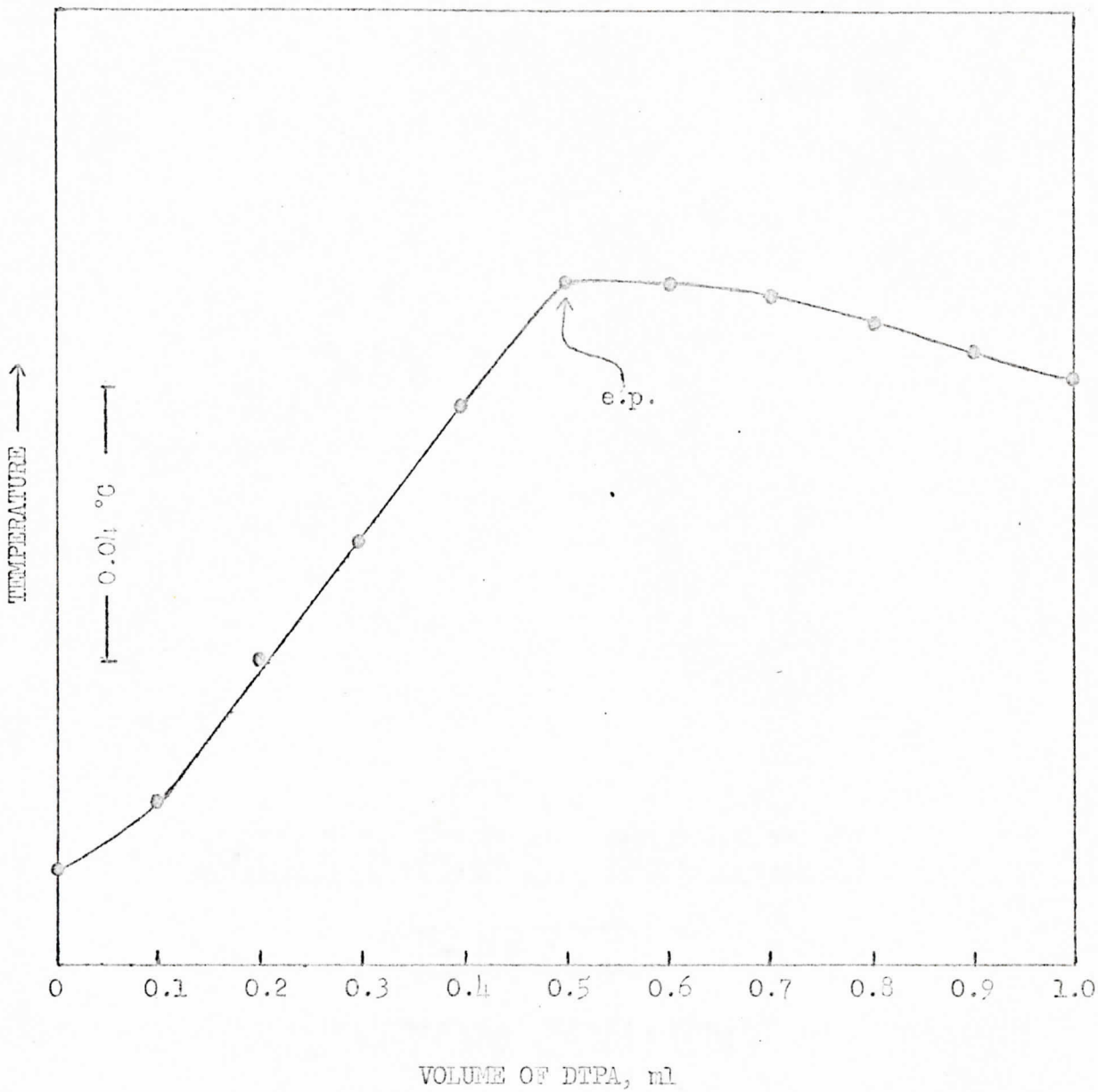


Figure 3

Titration of Pb^{2+} with DTPA

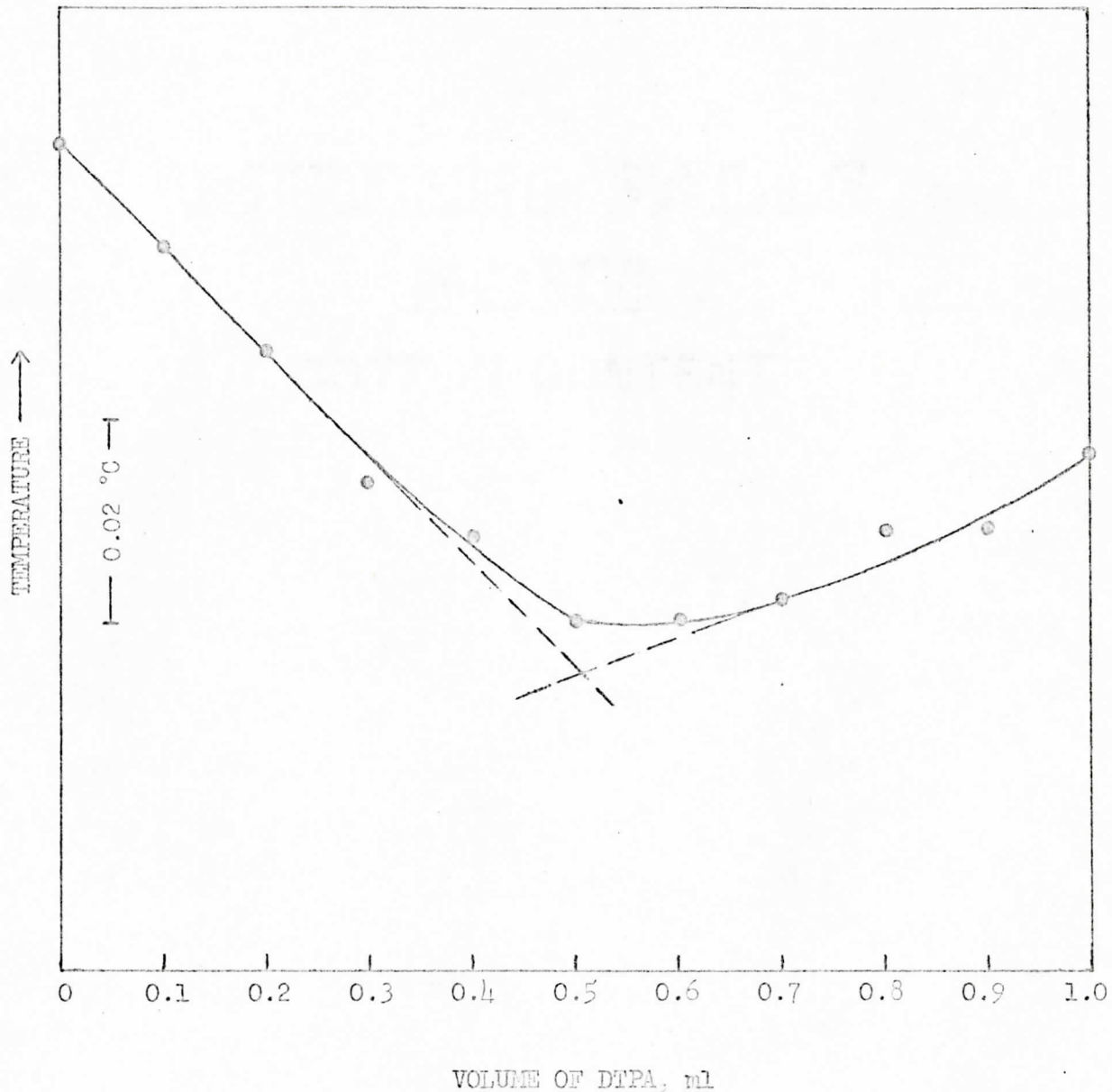


Figure 4

Titration of Mg^{2+} with DTPA

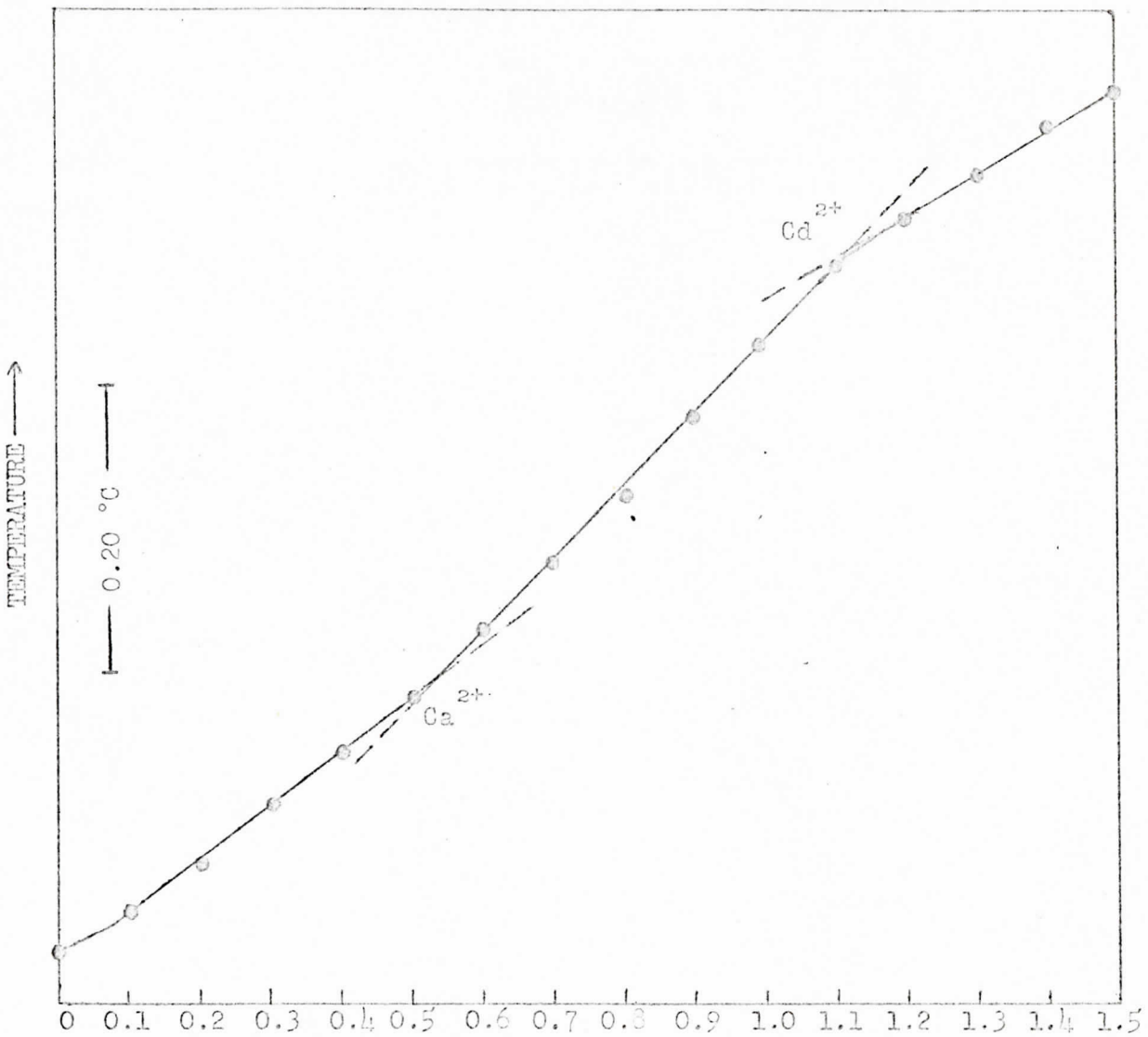


Figure 5

Titration of Ca^{2+}-Cd^{2+} Mixture with DTPA

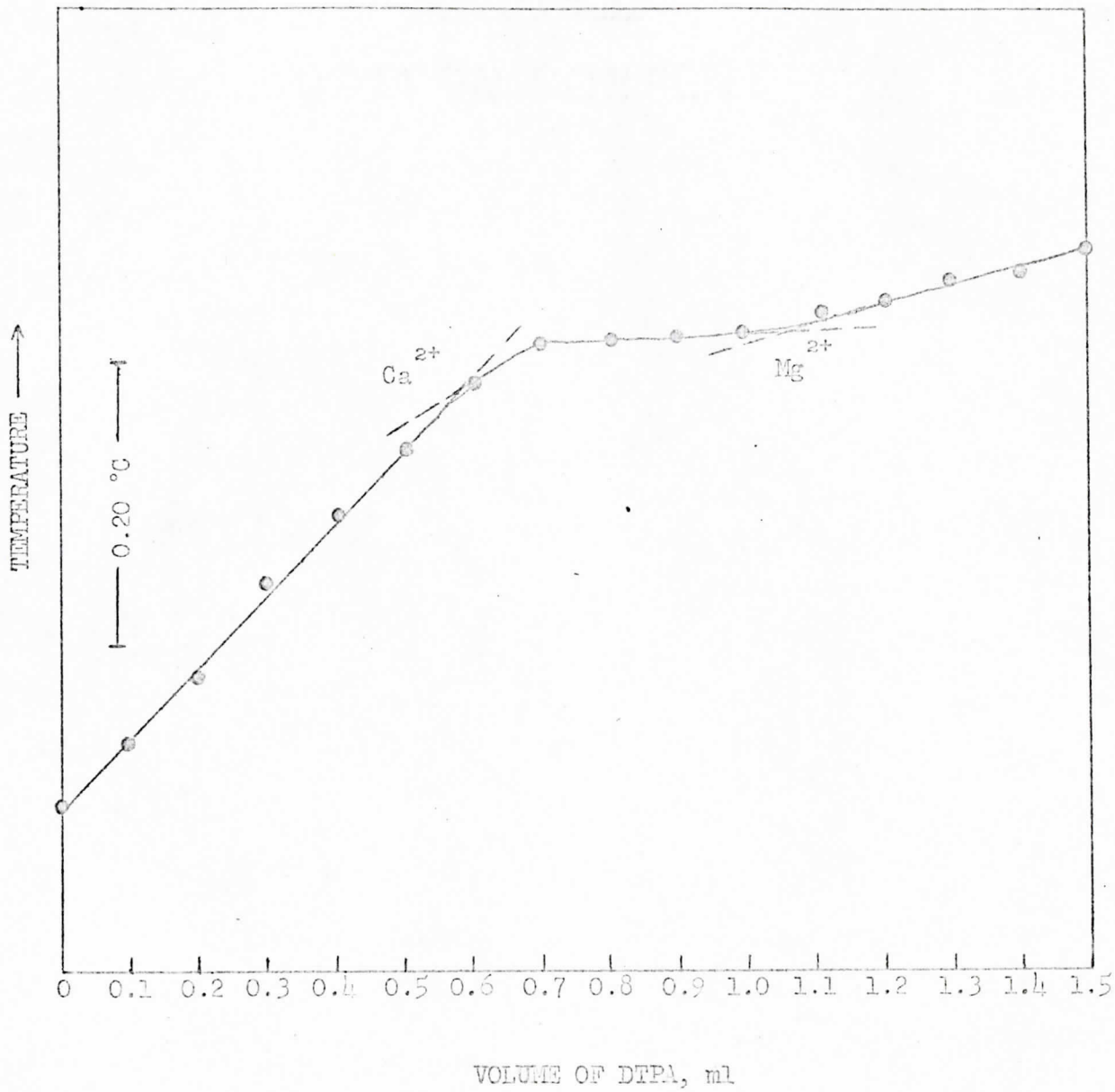


Figure 6

Titration of Ca^{2+}-Mg^{2+} Mixture with DTPA

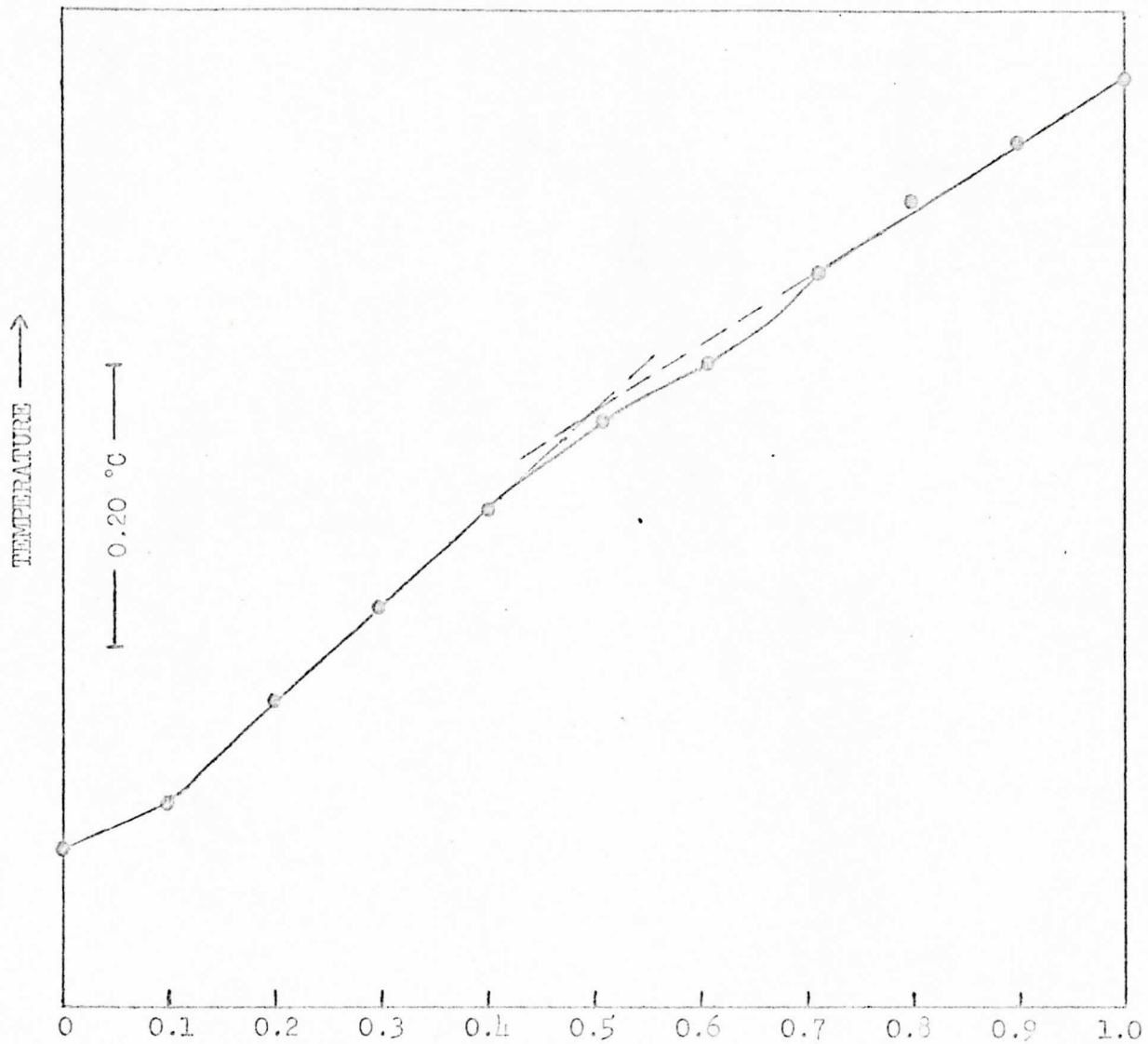


Figure 7

Titration of Ni^{2+} with DTPA

Ca^{2+} and Mg^{2+} which previously had been titrated thermometrically with EDTA (8), were found to meet these requirements. This titration is particularly interesting because the heat of formation for the Ca^{2+}-DTPA complex is exothermic while the heat of formation for the Mg^{2+}-DTPA complex is endothermic. Ca^{2+}, having a higher stability constant, is chelated first and the temperature rises. After all the Ca^{2+} is chelated the Mg^{2+} begins to react with the DTPA and the temperature of the solution decreases or in some instances levels off due to the slowness of the response of the Beckman thermometer. After the Mg^{2+} endpoint the curve either rises rapidly or drops rapidly depending on the difference in temperature between the titrant and the solution being titrated. This titration is also interesting because it is feasible even though the stability constants of the two ions differ by less than two orders of magnitude. This titration is shown in Figure 6.

The titration of the mixture of Ca^{2+} and Cd^{2+} gave results different from what was expected. Cd^{2+} has a heat of reaction with DTPA of -12.4 ± 0.5 kcal/mole while Ca^{2+} has a heat of reaction of -6.1 ± 0.4 kcal/mole. For the Cd^{2+}-DTPA complex the stability constant is larger than the Ca^{2+}-DTPA complex. These two factors indicate that the Cd^{2+}-DTPA complex should form first. However, if the titration is performed in the presence of several milliliters of ammonia buffer of pH = 10, it is found that Ca^{2+} will chelate first. This is evident from the shape of the titration curve which rises slowly during the first of the titration and then rises more rapidly after the first (Ca^{2+}) endpoint and finally gives a break in the curve which corresponds to the endpoint for Cd^{2+}. At the pH at which this titration was performed, Ca^{2+}-DTPA evidently has a higher effective stability constant

Table III

Titration of Single Ions with DTPA

Ion titrated	Millimoles taken	Millimoles found	Ratio	% error
Hg^{2+}	0.506	0.510	0.995	0.79
	0.507	0.522	0.975	2.96
	0.513	0.515	0.996	0.39
Pb^{2+}	0.527	0.515	1.022	2.38
	0.499	0.500	0.998	0.20
	0.512	0.516	0.994	0.78
Ni^{2+}	0.508	0.505	1.005	0.59
	0.499	0.500	0.998	0.20
	0.391	0.384	1.015	1.79
Zn^{2+}	0.390	0.380	1.028	2.58
	0.487	0.500	0.975	2.67
	0.495	0.505	0.982	2.20
Cd^{2+}	0.505	0.500	1.010	0.99
	0.502	0.503	0.990	0.80
	0.540	0.544	0.995	0.74
Co^{2+}	0.517	0.506	1.020	2.23
	0.492	0.480	1.025	2.44
	0.445	0.434	1.022	2.48
Mn^{2+}	0.516	0.512	1.008	0.79
	0.551	0.547	1.003	0.73
	0.523	0.520	1.005	0.58
Cu^{2+}	0.506	0.502	1.008	0.79
	0.506	0.502	1.008	0.79
	0.502	0.497	1.010	0.99
Ca^{2+}	0.519	0.524	0.992	0.96
	0.518	0.512	1.010	1.16
	0.519	0.516	1.005	0.58
Mg^{2+}	0.502	0.506	0.992	0.79
	0.502	0.510	0.986	1.59
	0.551	0.554	0.994	0.55

Table IV

Titration of Mixtures of Ions with DTPA

Ions Titrated A	B	Millimoles A Taken	Millimoles A Found	Ratio	% Error	Millimoles B Taken	Millimoles B Found	Ratio	% Error
Ca^{2+}	Mg^{2+}	0.518	0.512	1.010	1.16	0.502	0.512	0.982	1.98
Ca^{2+}	Mg^{2+}	0.520	0.524	0.995	0.77	0.502	0.500	1.005	0.40
Ca^{2+}	Mg^{2+}	0.530	0.532	0.998	0.38	0.528	0.527	1.002	0.19
Ca^{2+}	Cd^{2+}	0.524	0.532	0.985	1.52	0.528	0.537	0.985	1.67
Ca^{2+}	Cd^{2+}	0.551	0.556	0.991	0.91	0.536	0.528	1.012	1.49
Ca^{2+}	Cd^{2+}	0.446	0.452	0.988	1.34	0.478	0.487	0.983	2.30

than Cd^{2+}-DTPA.

An attempt was made to titrate a mixture of Cd^{2+} and Zn^{2+}. However, poor results were obtained because the formation constants of these two ions with DTPA are nearly the same.

A mixture of Hg^{2+} and Pb^{2+} was also titrated. In strongly acid solution an endpoint corresponding to the titration of Hg^{2+} could be obtained with an average error of 0.79% while in weakly acidic solution an endpoint corresponding to the sum of the two ions could be obtained with an average error of 2.45%. All attempts to obtain two endpoints in the same titration failed. However, a mixture of Hg^{2+} and Pb^{2+} can be determined indirectly by performing a set of two titrations--one to determine the sum of the two ions and the other to determine the amount of Hg^{2+} present. Then Pb^{2+} could be calculated by the difference.

The results of the various metal ion titrations were determined and tabulated as the ratio of millimoles taken to millimoles found. Also, the percentage error was calculated. An error of 3.0 per cent was regarded as the maximum permissable error. This is in keeping with results of previous investigators (3). The results are summarized in Tables 3 and 4.

Some of the titrations of single ions yield curves which were unusual in that they had three definite portions, each having a different slope. Such a curve is shown in Figure 7. Jordon and Alleman (3) reported this same irregularity and ascribed it to a thermistor characteristic. The appearance of this same anomaly in this work, in which a Beckmann thermometer was used to detect heat changes, shows that this is not a thermistor characteristic.

Conclusions:

The results of this investigation indicate that the thermometric technique is useful for endpoint detection in titrations of metal ions with DTPA. With proper instrumentation, titrations are completed rapidly and problems such as the blocking of an indicator are not encountered. The major difficulty involved is the adjustment of the pH of the metal ion solution to the required value prior to the titration. The results demonstrate that the efficiency of the chelating reaction is dependent on the pH of the solution.

By controlling the pH, titration of one metal ion in the presence of others is possible. This is indicated by the results of the titration of the Hg^{2+}-Pb^{2+} mixture. This mixture could be successfully determined by performing two titrations, one to determine the sum of the two ions and the other to determine the Hg^{2+}. The amount of Pb^{2+} present is determined by subtracting the amount of Hg^{2+} from the sum of the two ions. Probably similar procedures could be developed for other pairs of ions.

The success of the DTPA titrations in this investigation indicates that thermometric titrations with other polyaminocarboxylic acids will be practical. The use of a constant flow-rate buret to add the titrant, a thermistor to detect the temperature change, and a recorder to plot the resulting titration curve should increase the accuracy and precision of this method as well as allow for the titration of more dilute metal ion solutions.

One interesting use of thermometric titrations, when very accurate results are obtained, would be to determine the heats of formation of metal-chelates. According to Jordon and Alleman (8) this method is preferable to the classical type of calorimetric approach. Reasons given for this are:

(1) heats of dilution are corrected by a simple graphical extrapolation eliminating the need for "blank" experiments and (2) very dilute solutions can be used obviating corrections for infinite dilution.

Finally, future work to refine the technique, particularly towards analysis of more dilute metal ion solutions and to increase the application of the thermometric method to the titration of more mixtures would be useful. The determination of mixtures containing more than two ions should be possible. An example would be Ca^{2+}, Cd^{2+}, and Mg^{2+}. Other mixtures including Cd^{2+} and Zn^{2+} might be determinable if a thermistor were used to detect the slight changes in the slope of the titration curves, particularly in the region of the endpoints.

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